Treatment of Severe Infectious Purpura in Children with Human Plasma from Donors Immunized with *Escherichia coli* J5: A Prospective Double-Blind Study

J5 Study Group*

To evaluate the efficacy of anti-J5 serum in the treatment of severe infectious purpura, 73 children were randomized to receive either anti-J5 (40) or control (33) plasma. Age, blood pressure, and biologic risk factors were similar in both groups. At admission, however, tumor necrosis factor serum concentrations were 974 ± 173 pg/ml compared with 473 ± 85 pg/ml ($P = .023$) and interleukin-6 serum concentrations were 129 ± 45 compared with 19 ± 5 ng/ml ($P = .005$) in the control and treated groups, respectively. The duration of shock and the occurrence of complications were similar in both groups. The mortality rate was 36% in the control group and 25% in the treated group ($P = .317$; odds ratio, 0.76; 95% confidence interval, 0.46–1.26). This trend disappeared after correction for unbalances in risk factors at randomization using a logistic regression model. These results suggest that anti-j5 plasma did not affect the course or mortality of severe infectious purpura in children.

The J5 mutant of *Escherichia coli* O111:B4 is characterized by defective lipopolysaccharide lacking the O side chains responsible for specific antigenicity among gram-negative bacteria [1, 2]. Thus, this mutant presents on its surface a core glycolipid accessible for immunologic reactions [3]. In humans, immunotherapy with serum obtained after immunizing volunteers with *E. coli* J5 vaccine (J5 antiserum) decreased the mortality due to gram-negative bacteremia and shock [4]. In a study of prophylaxis, J5 antiserum prevented the development of septic shock in surgical patients [5].

Severe infectious purpura in children is most frequently due to *Neisseria meningitidis* and occasionally to *Haemophilus influenzae* type b. The clinical spectrum of *N. meningitidis* infections is broad, ranging from the asymptomatic carrier state to fulminant septicemia. Clinical and biologic risk factors have been described [6–9], allowing the identification of patients at high risk for death. Circulating concentrations of tumor necrosis factor-α (TNFα) also correlated with severity of disease [10] and outcome [11]. Meningococcal endotoxin has a crucial role in the pathogenesis of the disease [12], and circulating endotoxin concentrations have been shown to correlate with the development of multiple organ failure and death in patients with systemic meningococcal disease [13]. Animals challenged by meningococcal endotoxin were protected by antiserum raised against *E. coli* J5 [14]. Thus, severe infectious purpura in children represents a particular model of septic shock with a fulminant course in certain patients and a high mortality rate despite early antibiotic treatment and progress in supportive care [7, 15].

The aim of this double-blind randomized multicenter study was to analyze the effect of plasma obtained from volunteers after *E. coli* J5 immunization on the course and mortality of severe infectious purpura in children.

Methods

Preparations of anti-J5 plasma. Healthy donors were immunized with J5 vaccine (provided by E. J. Ziegler, University of California Medical Center, San Diego) as in the two previous successful trials [4, 5]. Nine volunteers were immunized in Lausanne, Switzerland and 800–900 ml of plasma was collected before immunization to provide control plasma and 2 weeks after immunization at the peak of hemagglutinating antibody response to provide anti-J5 plasma. When assessed by ELISA, this vaccination schedule induced a median 3.25-fold increase in anti-J5 lipopolysaccharide IgG and a 3.00-fold increase in IgM [16]. Citrated plasma was distributed in sterile blood-component packs, each containing 100 ml of plasma. These units were frozen at −70°C for 24 h and then kept at −20°C until used. Donors were serologically tested for syphilis (using VDRL antigen), hepatitis B surface antigen, and human immunodeficiency virus type 1 antibodies before immunization and 6 months later by the blood transfusion service of the Centre Hospitalier Universitaire Vaudois, in a similar fashion as regular blood donors. The plasma of a particular donor was not used until the results of a repeated serologic test were negative.

A computer-generated randomized list was established and plasma units were numbered so that investigators were unaware whether immune or control plasma was given to the patient.

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Use of anti-J5 plasma was approved by the ethics committees of the participating institutions.

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Each participating center received an equal number of control and anti-J5 plasma units grouped by pair. Because the randomization was done separately in each center, an equal number of patients was not reached in each group.

Clinical trial. The trial was conducted in pediatric intensive-care units of 14 French and 4 Swiss hospitals. Children eligible for inclusion were those with a clinical diagnosis of sepsis and with purpuric lesions. Children were enrolled in the study if they were in shock or if they had three or more of the biochemical abnormalities known to be biologic risk factors for poor prognosis in such patients: a leukocyte count of $<10.0 \times 10^9$/l, a platelet count of $<100.0 \times 10^9$/l, a fibrinogen level of <1.5 g/l, a serum CO_2 level of <15 mmol/l, and a cerebrospinal fluid cell count of $<0.1 \times 10^9$/l.

The definition of shock was based on the presence of two of the following: hypotension defined by values of systolic or diastolic pressure decreased by >2 SD for the age [17, 18], a peripheral skin recoloration time of >3 s, a decreased peripheral pulse amplitude, and the most recent micturition >6 h before admission. On admission, blood was obtained for determining the biologic risk factors and for bacterial cultures according to well-established methods [19]. Clinical assessment of shock was made on all the patients.

Once enrolled, patients were randomized and received intravenously over 30 min a single dose of 4 ml/kg of body weight (maximum dose, 100 ml) of either anti-J5 or control plasma. Before plasma was given, blood was drawn for determination of serum levels of anti-J5 lipopolysaccharide antibodies, TNFα, and interleukin-6 (IL-6). Six hours after the administration of the plasma, fibrinogen, total CO_2 content, white blood cell and platelet counts, anti-J5 lipopolysaccharide antibodies, and cytokine concentrations were again measured. Serum cytokine determinations were repeated on day 5. In all patients adapted antibiotics to repress *N. meningitidis* and *H. influenzae* were given for a minimum of 10 days. Hypotension was treated with intravenous fluids and the usual catecholamines if necessary. When hypoxemic, patients were intubated and ventilated. Complications were treated according to the best current practice.

End points. The principal end point of the study was the mortality rate. The occurrence of complications of the disease and the evolution of clinical and biologic parameters of the two groups were also compared.

Biochemical determinations. Serum TNFα was assayed with a competitive inhibition RIA (IRE; Medgenix, Fleurus, Belgium) as described [10]. Serum IL-6 was measured using IL-6–dependent mouse-mouse hybridoma cells, 7TD1 (provided by J. Van Snick, Ludwig Institute, Brussels) according to his method [20]. Anti-J5 lipopolysaccharide antibodies were measured with an ELISA as described [21].

Statistics. Every patient who received investigational therapy was included in the data analysis. In the initial planning of the trial, the number of patients required to show a decrease of mortality from 50% in the control group to 25% in the treated group was 86 [22] (α-error, 5%; β-error, 10%). To allow early detection of important differences in outcome between the two treatment groups, examination of the mortality rate at mid-study was planned. At this time, the observed mortality was 30% in the control group and 26% in the treated group. With the mortality observed in the control group, the requirement for patients to show a 50% decrease in mortality was then calculated to be 264 [22]. Because the incidence of the disease dropped from 42 patients per year in 1986 to 20 in 1987 and 11 in 1988, we decided to discontinue the study.

Data analysis. Statistical analysis of clinical and biologic data was done using Fisher's exact test for the comparisons of proportions and the Mann-Whitney test for comparing differences between the two groups. A logistic regression analysis was done using a BMDP statistical package [23]. Odds ratios were calculated as the exponential of the coefficient, with the outcome (death or survival) as dependent variable in the model. Values are given as mean ± SE. All reported significance levels were two-tailed.

Results

During a 3-year period, 73 patients were randomized into the study. Of these, 40 received the anti-J5 plasma and 33 the control plasma. A total of 48 patients had *N. meningitidis* isolated from blood cultures, cerebrospinal fluid cultures, or both (28 in the anti-J5, 20 in the control group; $P = .462$), and 2 patients had *H. influenzae* type b (1 in each group). Twenty-nine patients (19 [48%] in the treated group and 10 [30%] in the control group; $P = .327$) received a dose of antibiotics before or during transport to the hospital as soon as the clinical diagnosis of severe infectious purpura was made. Antibiotic treatment consisted of a third-generation cephalosporin in 45 patients and ampicillin in 28 patients. The distribution of the two antibiotic regimens was similar in the two treatment groups and was also similar between survivors and nonsurvivors.

The distribution of clinical and biologic baseline values is shown in table 1. The 11 parameters were comparable in the two groups. By contrast, patients in the control group had higher TNFα and IL-6 serum concentrations at admission than did those in the treated group. Figure 1 shows the correlation between serum IL-6 and TNFα concentrations according to treatment group and outcome. Of 8 patients who had both cytokines elevated, 7 belonged to the control group. Moreover, 11 of 33 patients had a fibrinogen concentration of <1.00 g/l in the control group and 5 of 40 in the treated group ($P = .032$). Thus, although at first glance the two groups appeared well balanced, several biologic factors showed that the control group might have been more severely affected. Of the 73 patients, 54 were hypotensive at admission: 25/(76%) of 33 in the control group and 29/(73%) of 40 in the treated group ($P = .795$). As hypotension represents a significant clinical risk factor for mortality and morbidity, the effect of anti-J5 treatment was analyzed in this subgroup of patients. Tables 2 and 3 summarize the results of treatment with anti-J5 plasma in the entire group of patients and in those who were hypotensive on admission. No difference was observed between the two treatment groups. The duration of hypotension, vasopressor therapy, and respira-

Table 1. Clinical and biologic parameters of control and treated children with severe infectious purpura before J5 administration.

Parameters	Controls (n)	Treated (n)	P*
Age, years	4.4 ± 0.7 (33)	4.2 ± 0.7 (40)	.387
Blood pressure, mm Hg			
Systolic	73 ± 5 (32)	72 ± 3 (38)	.836
Diastolic	44 ± 4 (20)	45 ± 3 (26)	.781
Leukocytes, 10⁹/l			
Peripheral blood	7.9 ± 1.5 (31)	8.1 ± 1.1 (40)	.525
Cerebrospinal fluid	0.37 ± 0.19 (25)	0.55 ± 0.20 (31)	.760
Fibrinogen, g/l	2.30 ± 0.32 (31)	2.59 ± 0.25 (36)	.324
Platelets, 10⁹/l	128.6 ± 23.8 (30)	138.7 ± 15.3 (40)	.285
Total CO_2, mmol/l	13.9 ± 0.9 (30)	16.1 ± 0.7 (37)	.135
Tumor necrosis factor, pg/ml	974 ± 173 (22)	473 ± 85 (26)	.023
Interleukin-6, ng/ml	129 ± 45 (21)	19 ± 5 (26)	.005
Intervals, h, from†			
First symptoms of disease to lesions	11.9 ± 1.7 (32)	14.7 ± 3.5 (40)	.858
Appearance of lesions to plasma administration	6.5 ± 0.8 (33)	7.5 ± 0.8 (40)	.221

NOTE. Data are mean ± SE.

* By Mann-Whitney.

† Intervals are hours from appearance of first symptoms (usually fever) and appearance of purpura and hours from appearance of purpuric lesions and the time plasma is given (anti-J5 or control).

tory assistance indicated that the time required for reversal of shock was similar in each treatment group. The occurrence of systemic complications of meningococcemia, skin necrosis requiring skin grafting, and amputations was also similar. Survival was not prolonged in the treated group: In nonsurvivors, the interval between plasma administration and death was ~1.5 days in both groups. The mortality rate was 36% in the control group and 25% in the treated group (P = .29), with an odds ratio of 0.76 in favor of the treated group (95% confidence interval, 0.46–1.26). In the patients who were hypotensive on admission, the evolution of the clinical and biologic parameters of each treatment group was similar to that observed for the entire group of patients. Table 4 shows the different odds ratios calculated when the independent variables, found by the logistic regression model to correlate significantly with outcome, were included step-by-step in the model. The slight trend in favor of the treated group disappeared when those variables were considered.

Serum concentrations of TNFα and IL-6 measured 6 h after randomization were significantly lower than those measured on admission. The magnitude of the decrease of the two cytokines was similar in the control and treated groups (figure 2). Anti-J5 lipopolysaccharide IgG serum levels were undetectable or very low in all patients at entry and did not increase significantly after plasma infusion. Mean anti-J5 lipopolysaccharide IgM serum levels were higher than IgG levels and similar in both groups. Mean anti-J5 lipopolysaccharide IgM levels increased from 25 ± 6 units/ml before randomization to 33 ± 9 units/ml 6 h after plasma infusion in the control group (P = .385) and from 34 ± 5 to 38 ± 6 units/ml in the treated group (P = .542).

Discussion

In this study, plasma from donors immunized with *E. coli* J5 did not change the course or mortality of severe infectious purpura in children. The time required for reversal of shock, the number of complications, and the rate of decrease of serum cytokine concentrations were similar in the control and treated groups. Among the patients who died, survival was not prolonged in the treated group. A slightly lower mortality rate was observed in the anti-J5 group. Although conventional biologic and clinical characteristics were similar in the two groups of patients (table 1), higher TNFα and IL-6 concentrations at admission indicated a trend toward more severely ill patients in the control group (figure 1). This was confirmed by a higher number of patients in the control group with extremely low fibrinogen concentrations. Both TNFα [10, 11] and IL-6 [24] circulating concentrations correlated with the severity of infectious purpura. IL-6 concentrations were increased in meningococcemia [24] and in experimental endotoxemia in humans [25].

The correlation in our study between the logarithm of IL-6

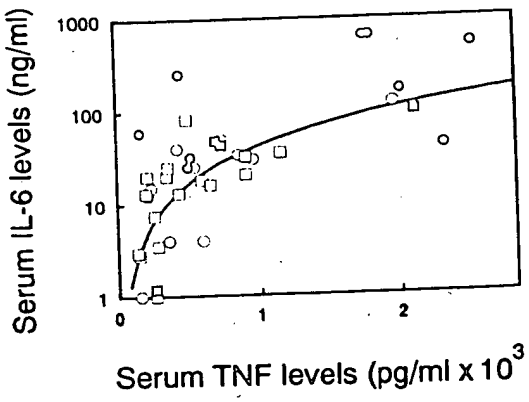

Figure 1. Correlation between serum interleukin-6 (Il-6) and serum tumor necrosis factor-α (TNF) concentrations before plasma treatment in control group (alive, ○; deceased, ○) and anti-J5 group (alive, □; deceased, □). Il-6 levels are plotted on logarithmic scale (r = .75, P < .001).

Table 2. Biologic parameters in control and anti-J5-treated groups of children with severe infectious purpura.

Parameter	Entire group			Hypotensive patients		
	Controls (*n*)	Treated (*n*)	*P*	Controls (*n*)	Treated (*n*)	*P*
Duration of Hypotension, h	7.8 ± 1.6 (33)	6.4 ± 1.4 (40)	.719*	8.2 ± 1.8 (25)	5.9 ± 1.5 (29)	.280*
Adrenergic therapy, h	46.9 ± 7.1 (33)	50.7 ± 7.4 (40)	.907*	49.7 ± 8.6 (25)	43.5 ± 6.1 (29)	.755*
Respiratory assistance, days	4.1 ± 1.2 (27)	2.7 ± 0.4 (29)	.850*	4.7 ± 1.5 (21)	2.3 ± 0.3 (21)	.516*
Skin graft, %	9 (33)	10 (40)	1.000†	8 (25)	7 (29)	1.000†
Amputation, %	6 (33)	10 (40)	.683†	4 (25)	14 (29)	.358†
Interval before death, days	1.6 ± .4 (12)	1.3 ± 0.2 (10)	.961*	1.7 ± 0.5 (10)	1.3 ± 0.3 (8)	.632*
Mortality, %	36 (33)	25 (40)	.317†	40 (25)	28 (29)	.394†

NOTE. Data are mean ± SE.
* By Mann-Whitney.
† By two-tailed Fisher's exact test.

and TNFα is compatible with secretion of IL-6 in response to TNFα, as found in vitro in endothelial cell cultures [26, 27]. The bias in distribution observed in our study could explain the difference in mortality in the two groups of patients, a hypothesis that was supported by the calculation of the odds ratios in a multiple logistic regression after introduction of the risk factors in the model (table 4). These data show that important prognostic factors such as TNFα and IL-6 can be unbalanced while other conventional biochemical and clinical characteristics appear to be similar. Thus, TNFα and IL-6 levels should be measured during studies of patients with infectious purpura or other types of septic shock.

The discrepancy between the success of antiserum to *E. coli* J5 in preventing and treating gram-negative septic shock in previous trials [4, 5] and the results observed in this study might have several explanations. First, infectious purpura is characterized by a fulminant course, and a rapid disappearance of circulating endotoxin has been described in this disease [13]. Thus, the timing of the administration of anti-J5 antibody might be critical. In our study, the mean interval between the onset of purpura and the plasma administration was very short (7 h in both treatment groups). Because this delay was certainly not longer than that in the previous successful studies, it is unlikely that the discrepant results of the

Table 3. Biologic parameters in control and anti-J5-treated groups of children with severe infectious purpura 6 h after treatment.

Parameter	Entire group			Hypotensive patients		
	Controls (*n*)	Treated (*n*)	*P*	Controls (*n*)	Treated (*n*)	*P*
Leukocytes, 10^9/l	16.6 ± 2.3 (22)	15.5 ± 1.5 (32)	.986	17.1 ± 2.8 (16)	15.3 ± 1.7 (22)	.882
Fibrinogen, g/l	3.00 ± 0.39 (21)	2.58 ± 0.25 (31)	.730	2.65 ± 0.41 (15)	3.00 ± 0.33 (21)	.320
Platelets, 10^9/l	101.3 ± 18.8 (21)	138.7 ± 15.3 (33)	.972	100.8 ± 24.7 (15)	100.7 ± 22.0 (23)	.881
Total CO_2, mmol/l	19.2 ± 0.9 (21)	16.1 ± 0.7 (29)	.609	18.3 ± 1.0 (15)	18.1 ± 1.1 (20)	.960

NOTE. Data are mean ± SE; *P* by Mann-Whitney.

Table 4. Influence of serum levels of fibrinogen, thrombocytes, tumor necrosis factor-α (TNFα), and interleukin-6 (IL-6) on the effect of J5 plasma on children with severe infectious purpura assessed by a logistic regression model.

Covariable	*n*	Logistic coefficient of J5 effect	SE	*P*	Odds ratio (95% CI)
None	73	−0.27	0.275	.29	0.76 (0.46–1.26)
Fibrinogen	67	−0.27	0.329	.41	0.76 (0.40–1.45)
+ thrombocytes	64	−0.17	0.363	.63	0.84 (0.41–1.72)
+ thrombocytes + IL-6	44	0.27	0.723	.71	1.30 (0.32–5.39)
+ thrombocytes + IL-6 + TNFα	43	0.47	0.838	.55	1.60 (0.31–8.27)

NOTE. Logistic regression analysis done using BMDP statistical package [23]. Coefficient of effect of treatment group (J5 plasma or control) on outcome computed first with only treatment group as independent variable in model and then after other independent variables (fibrinogen, thrombocytes, IL-6, and TNF) were forced step-by-step into model. Odds ratios calculated as exponentials of coefficients. Effect of treatment group not significant in all models tested. CI, confidence interval.

present study are due to delay in plasma administration. Second, in this study, the administration of 4 ml/kg of J5 plasma did not significantly increase anti-J5 lipopolysaccharide antibodies. This could be explained by the threefold increase of the antibody titers observed in the plasma of volunteers after immunization [16]. However, a comparable three- to fivefold increase in the titers of volunteers was observed in the two previous successful studies [4, 5]. Thus, the lack of detectable increase in anti-J5 lipopolysaccharide antibody in the recipients of J5 plasma could not account for the discrepant results, although some observations suggest that the magnitude of endotoxemia might be higher in meningococcal sepsis than in other types of gram-negative sepsis [13]. Third, there is no cross-protection between *E. coli* J5 antibodies and *N. meningitidis* or *H. influenzae* type b.

Up to now, the exact mechanism of the protection of J5 antiserum observed in the successful clinical studies is not known. In neither of the two successful studies using J5 antiserum could the outcome be convincingly related to anti-J5 lipopolysaccharide antibodies. In addition, two clinical studies using anti-core lipopolysaccharide intravenous immunoglobulins have been unsuccessful. One used J5 intravenous immunoglobulins prepared from donors immunized with *E. coli* J5 for the treatment of gram-negative shock [28]. The other study used anti-Re lipopolysaccharide intravenous immunoglobulins prepared after selection of donors with high naturally acquired anti-Re lipopolysaccharide antibodies for the prevention of gram-negative infection and shock in high-risk surgical patients [29]. In both studies, the lack of efficacy might have been attributed to the absence of anti-core lipopolysaccharide IgM antibodies in the preparations used, although the protective power of anti-core lipopolysaccharide IgM is controversial [30, 31]. Results of two recent clinical studies have suggested that the administration of anti-lipid A IgM monoclonal antibodies to patients with gram-negative sepsis might benefit some patients [32, 33], although these results should still be considered preliminary and controversial [34]. It is now recognized that there is significant heterogeneity among the core regions of lipopolysaccharide from various gram-negative bacteria, so that the conservation of the structure among core lipopolysaccharides from different gram-negative bacteria has been questioned. For example, the microheterogeneity of the core structure of the lipopolysaccharide from *E. coli* J5 has long been recognized [35]. Experimental data on the cross-reactivity of antibodies against core lipopolysaccharide with lipopolysaccharide extracted from other gram-negative bacteria have been contradictory [21, 36–41]. Recently, it was shown experimentally that core lipopolysaccharide antibodies did not prevent the production of endotoxin-induced cytokines, in contrast to O side chain–specific antisera, which decreased the production of both TNFα and IL-6 [42]. In the present study, the decrease of serum TNFα and IL-6 levels observed 6 h after

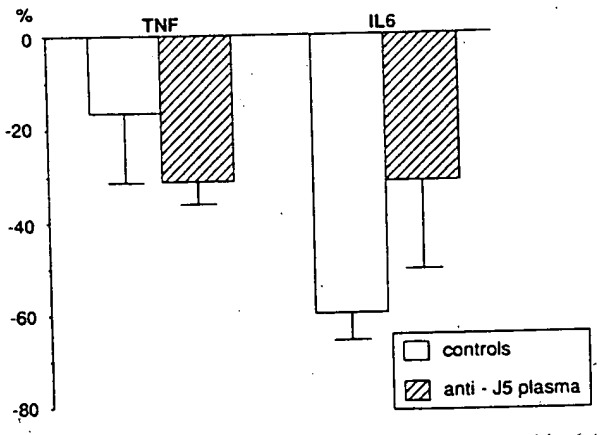

Figure 2. Tumor necrosis factor-α (TNF) and interleukin-6 (IL-6) serum concentrations expressed in percentage between prerandomization values and serum obtained 6 h after treatment in recipients of control and anti-J5 plasma.

plasma administration was similar in the control and treated groups.

Although the number of patients enrolled in this study was insufficient to rule out a β-error in view of the lower than expected mortality in the control group, the absence of impact of anti-J5 plasma on the clinical and biologic parameters and on the cytokine levels suggests that a clinically important benefit is unlikely in this disease. Other immunologic approaches directed against antigens of the causative bacteria or against mediators like TNFα released during infections might represent a more efficient way to reduce the important mortality of this disease.

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